

Effect of administration of intestinal anthelmintic drugs on haemoglobin: systematic review of randomised controlled trials

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ABSTRACT

Objective To evaluate the effect of routine administration of intestinal anthelmintic drugs on haemoglobin.

Design Systematic review of randomised controlled trials.

Data sources Electronic databases and hand search of reviews, bibliographies of books, and abstracts and proceedings of international conferences.

Study selection Included studies were randomised or quasi-randomised controlled trials using an intestinal anthelmintic agent in the intervention group, in which haemoglobin was evaluated as an outcome measure. Trials in which treatment for schistosoma (praziquantel) was given exclusively to the intervention group were excluded.

Results The search identified 14 eligible randomised controlled trials. Data were available for 7829 subjects, of whom 4107 received an anthelmintic drug and 3722 received placebo. The pooled weighted mean difference (random effect model) of the change in haemoglobin was 1.71 (95% confidence interval 0.70 to 2.73) g/l ($P<0.001$; test for heterogeneity: Cochran $Q=51.17$, $P<0.001$; $I^2=61\%$ (37% to 76%)). With the World Health Organization's recommended haemoglobin cut-offs of 120 g/l in adults and 110 g/l in children, the average estimated reduction in prevalence of anaemia ranged from 1.1% to 12.4% in adults and from 4.4% to 21.0% in children. The estimated reductions in the prevalence of anaemia increased with lower haemoglobin cut-offs used to define anaemia.

Conclusions Routine administration of intestinal anthelmintic agents results in a marginal increase in haemoglobin (1.71 g/l), which could translate on a public health scale into a small (5% to 10%) reduction in the prevalence of anaemia in populations with a relatively high prevalence of intestinal helminthiasis.

INTRODUCTION

Anaemia is estimated to affect nearly a third of the global population,¹ and iron deficiency is believed to be the most important causal factor. However, whether iron intervention can control anaemia on a public health scale is increasingly being questioned. A recent systematic review of iron supplementation in children estimated that between 38% and 62% of baseline anaemia is responsive to iron supplementation among children aged under 6; the corresponding range for malarial hyperendemic regions is 6% to 32%.²

Administration of intestinal anthelmintic agents has been proposed as an additional intervention to reduce anaemia. Around two billion people globally are estimated to be infested with helminths.³ Observational data suggest an inverse relation between intestinal helminthiasis and haemoglobin concentrations.⁴ Intervention trials using anthelmintic drugs have provided conflicting evidence; some authors have documented improvements in haemoglobin concentration,^{w1 w2} whereas other investigators have found no such benefit.^{w3-w5} We did a systematic review of randomised controlled trials to evaluate the effect of routine administration of intestinal anthelmintic agents on haemoglobin.

METHODS

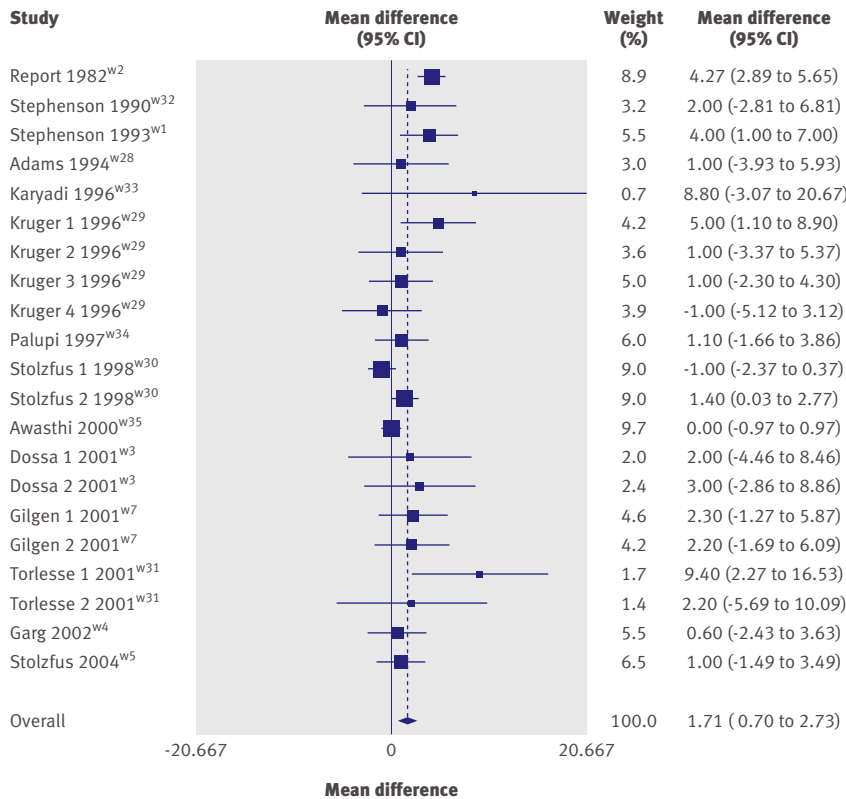
Searches—We ran Medline searches (1966 to 31 July 2006) using search words including haemoglobin, anaemia, deworming, anthelmintic, mebendazole, praziquantel, pyrantel, piperazine, nitazoxanide, levamisole, albendazole, bephenium, and niclosamide. We did a similar search of the Cochrane controlled trials register. We imposed no language restrictions. We reviewed reference lists of identified articles and hand searched reviews, bibliographies, and abstracts of international conferences. We scanned abstracts of the trials to exclude studies that were irrelevant. We scrutinised the full texts of the remaining studies and identified trials that fulfilled the inclusion criteria.

Selection criteria—Trials had to be randomised or quasi-randomised and controlled, use an intestinal anthelmintic drug in the intervention group, and evaluate haemoglobin as an outcome measure. We considered studies in which other micronutrients and drugs were simultaneously administered to be eligible if the only difference between the intervention and control groups was the intestinal anthelmintic drug. We excluded trials in which treatment for schistosoma was given exclusively to the intervention group.

Validity assessment—We assessed the quality of trials by using recommended criteria.^{5,6} We considered concealment of allocation, percentage of participants lost to follow-up, and blinding.

Data abstraction—Two researchers used pre-formed questionnaires to abstract the data in duplicate.

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Forest plot of haemoglobin with unknown standard deviations derived with assumption (P)=0.5

Quantitative data synthesis—For calculating pooled estimates, we used or derived from available data the sample size, the mean change in haemoglobin or serum ferritin from the beginning to the end of the intervention, and the standard deviation of this change in the intervention and control groups (see bmj.com). We calculated the pooled estimates of the weighted mean difference of the evaluated change in outcome variable between the control and intervention group by both fixed effects and random effects model assumptions. We carried out prespecified stratified analyses for age group, developing or developed country, malaria endemicity, schistosoma endemicity, pre-intervention worm load, methodological quality,

compliance monitoring, number of anthelmintic courses, co-administration of iron, baseline haemoglobin concentrations, and baseline anthropometry (in children).

RESULTS

We identified 36 potentially eligible randomised controlled trials. Twenty two studies were ineligible.^{w6-w27} We evaluated 14 trials in this systematic review (see bmj.com).^{w1-w5 w28-w36}

Study characteristics

Table A on bmj.com summarises the baseline characteristics of the included trials. These studies were primarily done in developing countries on pre-school-children and schoolchildren (11/14). One study was done in non-pregnant adult women, one in pregnant women, and one in all age groups. Ten of the studies used albendazole as the anthelmintic drug, three used mebendazole, and one used bephenium. Iron was used as co-intervention in more than half of the studies (7/12). Twelve studies were done in areas classified as endemic for malaria, and six were done in areas endemic for schistosoma.

Quantitative data synthesis

We found no evidence of asymmetry of the funnel plot, suggesting an absence of publication bias (see bmj.com). We confirmed this by using the Egger’s (weighted regression) method (P for bias=0.11) and the Begg’s (rank correlation) method (continuity corrected P=0.11).

Data were available for 7829 patients, of whom 4107 received deworming treatment and 3722 received placebo. The pooled weighted mean difference (random effects model) of the change in haemoglobin (pre-intervention to post-intervention difference) after deworming was 1.71 (95% confidence interval 0.70 to 2.73) g/l (P<0.001; test for heterogeneity: Cochran Q=51.17, P<0.001; I²=61%, (37% to 76%)) (figure, table B on bmj.com). Other markers of iron status were estimated in only three of the studies,^{w5 w30 w31} which precluded a formal meta-analysis.

Sensitivity analyses (table B on bmj.com) suggested a greater rise in haemoglobin (non-overlapping confidence intervals) in trials that included adults. Meta-regression (see bmj.com) by univariate analysis suggested that inclusion of adults and use of iron as a co-intervention were significant predictors of a positive effect of the deworming agent. However, on multivariate analysis, neither of these variables was identified as a significant predictor.

We estimated the average expected reduction in the prevalence of anaemia with deworming on the basis of the calculated weighted mean difference at varying haemoglobin cut-offs (table). With the World Health Organization’s recommended haemoglobin cut-offs of 120 g/l in adults and 110 g/l in children, the average estimated reduction in the prevalence of anaemia ranged from 1.1% to 12.4% in adults and from 4.4% to 21.0% in children.

Estimated effects of deworming in reducing baseline anaemia prevalence (%) as defined by various cut-offs

Assumption	Haemoglobin (g/l) cut-off for defining anaemia			
	90	100	110	120
Low haemoglobin response				
Range	4.5-17.7	3.0-13.3	1.8-9.0	0.4-5.1
Mean (SE)	9.4 (0.6)	6.5 (0.5)	4.0 (0.3)	2.1 (0.2)
Average haemoglobin response				
Range	10.9-38.3	7.4-29.9	4.4-21.0	1.1-12.4
Mean (SE)	21.5 (1.3)	15.4 (1.1)	9.7 (0.8)	5.1 (0.5)
High haemoglobin response				
Range	17.1-54.2	11.8-43.8	7.2-32.0	2.0-19.6
Mean (SE)	32.2 (1.8)	23.6 (1.5)	15.3 (1.2)	8.3 (0.8)

WHAT IS ALREADY KNOWN ON THIS TOPIC

Anaemia is a widespread public health problem with major consequences for human health, as well as for social and economic development

Iron deficiency is believed to be the most important causal factor for anaemia, but whether iron intervention alone can control anaemia on a public health scale is questionable

Administration of intestinal anthelmintic drugs has been proposed as an additional intervention to reduce anaemia

WHAT THIS STUDY ADDS

Routine administration of intestinal anthelmintic drugs results in a marginal increase in haemoglobin concentration

On a public health scale, this could translate into a small (5% to 10%) reduction in the prevalence of anaemia in populations with a relatively high prevalence of intestinal helminthiasis

DISCUSSION

The results from these largely heterogeneous data derived from randomised controlled trials show that deworming without previous screening marginally improves haemoglobin concentration (weighted mean difference 1.71 (95% confidence interval 0.70 to 2.73) g/l, $P < 0.001$). Inclusion of adults and co-administration of iron emerged as significant univariate predictors of greater haemoglobin response and heterogeneity requiring further exploration. The projections of expected average reductions in baseline anaemia through routine deworming ranged from 5% to 10%.

Strengths and limitations

The main conclusion about the rise in haemoglobin after routine administration of intestinal anthelmintic agents remained stable over a large spectrum of sensitivity analyses. Influence analysis—namely, the effect of omitting one study at a time (data not shown)—did not reveal an overwhelming effect of any single trial.

Several limitations merit consideration. Firstly, most of the trials did not specifically evaluate the iron status of the patients. Secondly, in trials with missing data on the variability of the change in haemoglobin, we made several imputations on the basis of the prespecified assumptions. The sensitivity analysis suggested that these imputations were robust. Finally, we did multiple subgroup and meta-regression analyses for prespecified variables, which increased the possibility of false positive results. The identified significant predictors of greater haemoglobin response and heterogeneity should therefore be considered as only exploratory in nature, rather than definitive.

Implications

A few interesting observations emerged that can provide direction for future research. The baseline helminthic prevalence did not emerge as a significant predictor of haemoglobin response. This may have been because the egg density would be a better quantification of the helminthic load than single prevalence data. Alternatively, the host could have dynamically regulated the iron absorption in relation to the presence or absence of intestinal helminths.

An increase in the number of doses of anthelmintic agent was not a significant predictor of haemoglobin response. Further trials could include information on the time sequence of helminthic reinfection and haemoglobin concentrations to gain better insight into this observation. Another systematic review also could not document a greater effect on mean weight change in children with multiple doses of anthelmintics.⁷

Projections suggested that this marginal increase in haemoglobin could translate into a small (5% to 10%) reduction in the prevalence of anaemia on a public health scale. No leads emerge regarding the optimal frequency and periodicity of anthelmintics. Additional important aspects influencing public health decisions would include evaluation of other benefits, such as growth and cognitive performance,⁷ and adverse effects of routine administration of anthelmintics. Economic considerations of routine anthelmintic treatment, particularly in combination with iron prophylaxis, are also important. Considering the projected reductions in the prevalence of anaemia, the cost effectiveness would be unlikely to be substantial.

Conclusion

Routine administration of intestinal anthelmintic drugs results in a marginal increase in haemoglobin (1.71 g/l), which could translate on a public health scale into a small (5% to 10%) reduction in the prevalence of anaemia in populations with a relatively high prevalence of intestinal helminthiasis.

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Ethical approval: Not needed.

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